FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
217550US0PCT	10/031371

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/06545	10 JULY 2000	19 JULY 1999

TITLE OF INVENTION

SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

APPLICANT(S) FOR DO/EO/US

Maria C. GERONI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice of Priority / PCT/IB/304 / PCT/IB/308
PTO-1449

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/031371	PCT/EP00/06545	217550US0PCT

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$130.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	13 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $84.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	

TOTAL OF ABOVE CALCULATIONS =	**$1,020.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	**$0.00**	
SUBTOTAL =	**$1,020.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	**$0.00**	
TOTAL NATIONAL FEE =	**$1,020.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	**$0.00**	
TOTAL FEES ENCLOSED =	**$1,020.00**	
	Amount to be: refunded	$
	charged	$

a. ☒ A check in the amount of **$1,020.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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24,618
REGISTRATION NUMBER

Jan 18 2002
DATE

217550US-0 PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

MARIA C. GERONI ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW U.S. PCT APPLN :
(BASED ON PCT/EP00/06545)

FILED: HEREWITH :

FOR: SYNERGISTIC COMPOSITION
COMPRISING DAUNORUBICIN
DERIVATIVES AND
ANTIMETABOLITE COMPOUNDS

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please cancel Claims 9-11.

Please amend the claims as shown on the marked-up copy following this amendment to read as follows.

3. (Amended) A product according to claim 1 wherein the antimetabolite compound is a cytidine analog.

4. (Amended) A product according to claim 1 wherein the antimetabolite compound is a 5-fluoropyrimidine.

Please add the following new claims.

12. (New) A method for treating tumors in a mammal, including a human, in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in claim 1 and an antimetabolite compound to said mammal, including a human, in a synergistic antineoplastic effective amount.

13. (New) The method as claimed in claim 12 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

14. (New) A method for the treatment of metastasis in a mammal, including a human, in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in claim 1 and an antimetabolite compound to said mammal, including a human, in a synergistic antineoplastic effective amount.

15. (New) A method for the prevention of metastasis in a mammal, including a human, in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in claim 1 and an antimetabolite compound to said mammal, including a human, in a synergistic antineoplastic effective amount.

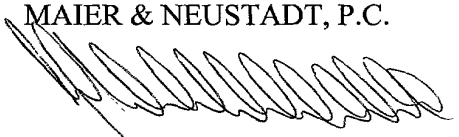
16. (New) A method for treating a tumor by the inhibition of angiogenesis in a mammal, including a human, in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in claim 1 and an antimetabolite compound to said mammal, including a human, in a synergistic antineoplastic effective amount.

REMARKS

Claims 1-9 and 12-16 are active in the present application. Claims 9-11 have been canceled. Claims 3 and 4 have been amended to remove multiple dependencies. Claims 12-16 are new claims. Support for the new claims is found in the original claims and in the specification on page 2, line 19 through page 3, line 26. No new matter is added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Marked-Up Copy
Serial No: _____
Amendment Filed on:
1-18-2002

IN THE CLAIMS

--3. (Amended) A product according to claim 1 [or 2] wherein the antimetabolite compound is a cytidine analog.

4. (Amended) A product according to claim 1 [or 2] wherein the antimetabolite compound is a 5-fluoropyrimidine.

Claims 9-11 (Canceled).

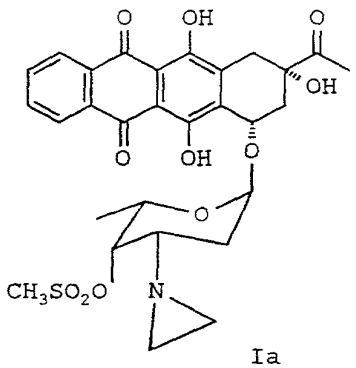
Claims 12-16 (New).

SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

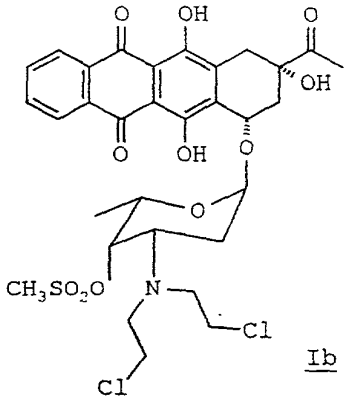
The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and an antimetabolite compound, having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an alkylating anthracycline of formula Ia or Ib :



Ia



Ib

- an antimetabolite compound, and a pharmaceutically acceptable carrier or excipient.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N7 position in DNA major groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of

cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

Antimetabolites are described in various scientific publications. The main representatives of this wide class of drugs are: the antifolates such as methotrexate, raltitrexed and trimetrexate; the 5-fluoropyrimidine compounds such as 5-fluorouracil, floxuridine and capecitabine; the cytidine analogs like cytarabine, azacitidine and gemcitabine. See for example the review: Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 432-452. The 5-fluoropyrimidine compounds and the cytidine analogs are the preferred antimetabolite compounds to be used in the present invention, more preferably 5-fluorouracil or gemcitabine. The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, in amounts effective to produce a synergistic antineoplastic effect.

The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antimetabolite compound as defined above and an alkylating anthracycline of formula Ia or Ib, as defined above, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor,

preferably the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a antimetabolite compound to mammals, including human. By the term "administered " or "administering" as used herein is meant parenteral and /or oral administration. By "parenteral" is meant intravenous, subcutaneus and intramuscolar administration. In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the compound with the antimetabolite compound activity, for example of the 5-fluoropyrimidine or cytidine class, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the alkylating anthracycline of formula Ia or Ib being utilized, the particular formulation of the antimetabolite compound, such as one of the 5-fluoropyrimidine or cytidine class, being utilized, the particular tumor model being treated, and the particular host being treated.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the antimetabolite compound the course of therapy generally employed is from about 0.1 to about 10 g/m^2 of body surface area. More preferably, the course therapy employed is from about 1 mg/m^2 to about 5 g/m^2 of body surface area. The antineoplastic therapy of the present invention is in particular suitable for treating breast, ovary lung,

colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an effective amount of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound in the prevention or treatment of metastasis or for the treatment of tumors by angiogenesis inhibition, as well as to the use of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis.

As stated above, the effect of an alkylating anthracycline of formula Ia or Ib and an antimetabolite compound, such as a 5-fluoropyrimidine or cytidine derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and of the antimetabolites and thus yields the most effective and least toxic treatment for tumors.

The superadditive actions of the combination preparation of the present invention may be shown for instance by in vivo tests for the antileukemic activity on disseminated L1210 murine leukemia. The combination of Ia with gemcitabine (Table 1) or 5-Fluorouracil tested at the different doses and schedules, produces favorable ILS% values (Increase in life span: [(median survival time of treated mice/median survival time of controls)x 100]-100), indicating a synergistic effect.

Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia obtained by combining the above PNU 159548 derivative with gemcitabine.

At the dose of 15 and 60 mg/kg of gemcitabine alone (ip day 1 after tumor injection) and at the dose of 1 and 1.5 mg/kg of PNU 159548 alone (iv day 1 after tumor injection, administered 2h after gemcitabine) were associated, without toxicity, with ILS% values of 50 and 83 and 33 and 67, respectively. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were observed, indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, respectively.

Table 1: Antileukemic activity against disseminated L1210[1] murine leukemia of PNU-159548 (I) in combination with gemcitabine

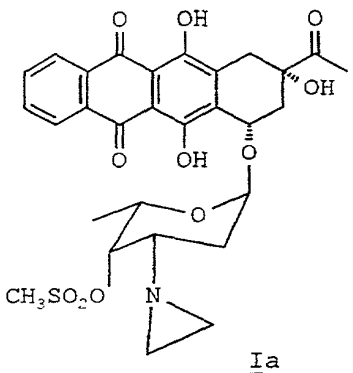
Compound	Treatment schedule	Dose (mg/kg/day)	ILS%[2]	LTS[3]	TOX[4]	CI[5]
PNU 159548	iv +1(*)	1 1.5	33 67	0/10 0/20	0/10 0/20	NA NA
Gemcitabine	ip +1	15 60	50 83	0/10 0/20	0/10 0/20	NA NA
PNU 159548 + gemcitabine	iv +1(*) ip +1	1 + 15 1.5 + 60	117 204	0/10 4/20	0/10 2/20	1.4 1.3

1. L1210 leukemia cells (10^5/mouse CD2F1) are injected IV on Day 0.
2. Increase in life span: [(median survival time of treated mice/median survival time of controls) x 100] -100.
3. LTS: long-term survivors (>60 days) at the end of the experiments
4. Number of toxic deaths/number of mice.
5. C.I. = combination Index : <1 antagonistic; 1 additive; >1 synergistic
   (*)administered 2h after gemcitabine
   NA: not applicable

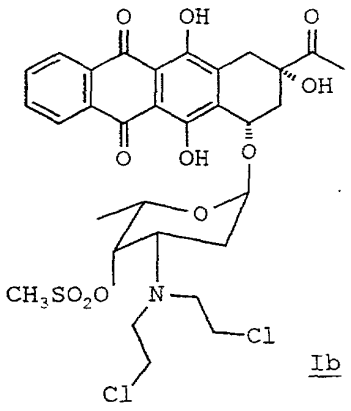
For these experiments Ia was solubilized in [Cremophor® /EtOH = 6.5:3.5]/[normal saline]=20/80 v/v, while standard pharmaceutical preparation were used for the antimetabolite compounds.

Claims

1. A product containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antimetabolite compound as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. A product according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin.

3. A product according to claim 1 or 2 wherein the antimetabolite compound is a cytidine analog.

4. A product according to claim 1 or 2 wherein the antimetabolite compound is a 5-fluoropyrimidine.

5. A product according to claim 3 wherein the cytidine analog is gemcitabine.

6. A product according to claim 4 wherein the 5-fluoropyrimidine is 5-fluorouracil.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound.

8. A composition according to claim 7 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the treatment of tumors.

10. Use according to claim 8 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

11. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(72) Inventors; and

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

(57) Abstract: The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and an antimetabolite compound in the treatment of tumors, especially in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis.

Declaration and Power of Attorney for Patent Application
Dichiarazione e procura ai fini della domanda di brevetto

Italian Language Declaration

Il sottoscritto inventore dichiara che:

As a below named inventor, I hereby declare that:

La propria residenza, recapito postale e cittadinanza corrispondono a quanto indicato in calce, sotto la propria firma.

My residence, post office address and citizenship are as stated next to my name.

Ritiene di essere il primo ed unico inventore originale (se viene elencato in calce un solo nominativo) o il coinventore primo ed originale (se è elencato più di un nominativo) del oggetto rivendicato e per il quale il sottoscritto presenta domanda di brevetto. La invenzione in questione è chiamata.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

e la sua descrizione è allegata alla presente Dichiarazione a meno:

the specification of which:

☐ è qui allegato

☐ is attached hereto.

☐ Il _____ è stata depositata una domanda di brevetto statunitense numero o una domanda di brevetto internazionale PCT numero _____ che è stata modificata il _____ (se applicabile).

XX was filed on January 18, 2002 ✓ as United States Application Number or PCT International Application Number 10/031,371 ✓ and was amended on _____ (if applicable).

Il sottoscritto dichiara in oltre di aver letto e compreso il contenuto della descrizione identificata in precedenza, rivendicazioni comprese, come modificati dall'eventuale modifica summenzionata.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Il sottoscritto riconosce l' obbligo di rivelare informazioni essenziali ai fini della determinazione della brevettabilità ai sensi del Titolo 37, Codice dei Regolamenti Federali, § 1.56.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Italian Language Declaration

Il sottoscritto rivendica con la presente la priorità prevista dal Titolo 35, Codice degli Stati Uniti, § 119(e)-(d) o § 365(b) in relazione a qualsiasi domanda o domande estere di brevetto o certificato di inventore, o dal Titolo 35, § 365(a) degli stessi Codice in relazione a qualsiasi domanda internazionale PCT nella quale è designato almeno un paese diverso dagli Stati Uniti, i suddetti domande e certifcati essendo elencati sotto, e, spuntando les seguenti caselle, ha anche identificato sotto qualsiasi domanda estera di brevetto o certificato di inventore, o domanda internazionale PCT, la cui data di deposito preceda quella dalla domanda per la quale è rivendicata la priorità.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) (Domande Estere Anteriori)			Priority claimed Diritto di priorità rivendicato	
9916882.5 ✓ (Number) (Numero)	Great Britain ✓ (Country) (Nazione)	19 July 1999 ✓ (Day/Month/Year Filed) (Giorno/Mese/Anno di deposito)	☒ Yes Sì	☐ No No
(Number) (Numero)	(Country) (Nazione)	(Day/Month/Year Filed) (Giorno/Mese/Anno di deposito)	☐ Yes Sì	☐ No No

Il sottoscritto rivendica con la presente i benefici previsti dal Titolo 35, Codici degli Stati Uniti, § 119(e), in relazione a qualsiasi domanda o domande provvisorie degli Stati Uniti elencate sotto.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (Nº della domanda)	(Filing Date) (Data di deposito)	(Application No.) (Nº della domanda)	(Filing Date) (Data di deposito)

Il sottoscritto rivendica con la presente i benefici previsti dal Titolo 35, Codice degli Stati Uniti, § 120, in relazione a qualsiasi domanda o domande statunitensi, o dal Titolo 35, § 365(c) degli stessi Codice in relazione a qualsiasi domanda internazionale PCT nella quale sono designati gli Stati Uniti, i suddette domande essendo elencate sotto e, nella misura in cui l'oggetto di ciascuna rivendicazione di questa domanda non sia stato esposto nella domanda statunitense o internazionale PCT anteriore nel modo previsto dal primo paragrafo del Titolo 35, Codice degli Stati Uniti, § 112, riconosce l'obbligo di rivelare informazioni essenziali ai fini della determinazione della brevettabilità ai sensi del Titolo 37, Codici dei Regolamenti Federali, § 1.56, le quali diventino disponibili durante il periodo compreso tra la data di deposito della domanda anteriore e la data di deposito nazionale o internazionale PCT della presente domanda.

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (Nº della domanda)	(Filing Date) (Data di deposito)	(Status) (patented, pending, abandoned) (Stato) (concessione di brevetto, in corso di esame, abbandono)
(Application No.) (Nº della domanda)	(Filing Date) (Data di deposito)	(Status) (patented, pending, abandoned) (Stato) (concessione di brevetto, in corso di esame, abbandono)

Con la presente, il sottoscritto dichiara veritiere tutte le affermazioni contenute in questa domanda in relazione alle proprie conoscenze e di ritenere vere tutte le affermazioni o informazioni presentate. Dichiara inoltre che tali asserzioni sono state espresse nella piena consapevolezza che le dichiarazioni intenzionalmente false sono punibili con una poulte, l' incarcerazione o entrambe, ai sensi della Sezione 1001 del Titolo 18 del Codice degli Stati Uniti e che tali dichiarazioni entenzionalmente false possono mettere a repenfaglio la validità della domanda o di qualsiasi brevetto ruasciato in merito.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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PROCURA: Il sootscritto inventore nomina con la presente il seguente avvocato o avvocati e/o agente o agenti al fine di istruire questa pratica e di condurre tutte le operazione ad essa pertinenti presso l'Ufficio dei Brevetti e Marchi di Fabbrica: (Elencare il nome ed il numero di matricola).

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

Inviare le corrispendenza a:

Send Correspondence to:

Telefonare a:
(Nome e numero telefonico)

Direct Telephone calls to: *(name and telephone number)*

(703) 413-3000

Nome e cognome dell'unico o del primo inventore 1-00	Full name of sole or first inventor Maria Cristina Geroni
Firma dell'inventore Data	Inventor's signature Date Maria Cristina Geroni March 4, 2002
Residenza	Residence Milano, Italy ITX
Cittadinanza	Citizenship Italian ✓
Recapito postale	Post Office Address Via Correggio 48, 20149 Milano, Italy
Nome e cognome dell'eventuale secondo coinventore 2-00	Full name of second joint inventor, if any Marina Ripamonti
Firma del secondo coinventore Data	Second inventor's signature Date Marina Ripamonti March 4, 2002
Residenza	Residence Milano, Italy ITX
Cittadinanza	Citizenship Italian ✓
Recapito postale	Post Office Address Viale Fulvio Testi 91, 20162 Milano,
	Italy

(Fornire le stesse informazioni e le firme del terzo e degli ulteriori coinventori.)

(Supply similar information and signature for third and subsequent joint inventors

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Nome per intero di un eventuale terzo co-inventore	Full name of third joint inventor, if any
3-00	Michele Caruso
Firma del Terzo Inventore Data	Third inventor's signature Date March 4, 2002
Residenza	Residence Milano, Italy ITX
Cittadinanza	Citizenship Italian
Recapito postale	Post Office Address Via Desiderio 3, 20131 Milano, Italy
Nome per intero di eventuale quarto co-inventore	Full name of fourth joint inventor, if any
4-00	Antonino Suarato
Firma Quarto Inventore Data	Fourth inventor's signature Date March 4, 2002
Residenza	Residence Milano, Italy ITX
Cittadinanza	Citizenship Italian
Recapito postale	Post Office Address Via Degli Imbriani 39, 20158 Milano,
	Italy
Nome per intero di un eventuale quinto co-inventore	Full name of fifth joint inventor, if any
Firma Quinto Inventore Data	Fifth inventor's signature Date
Residenza	Residence
Cittadinanza	Citizenship
Recapito postale	Post Office Address
Nome per intero di un eventuale sesto co-inventore	Full name of sixth joint inventor, if any
Firma del Sesto Inventore Data	Sixth inventor's signature Date
Residenza	Residence
Cittadinanza	Citizenship
Recapito postale	Post Office Address

(Si prega di fornire simili informazioni e firme peril terzo e gli eventuali ulteriori co-inventori.)

(Supply similar information and signature for third and subsequent joint inventors.)